REMARKS

Claims 1-5, 9-12, 14-19, 22-25, 29-35, and 39-41 are pending in the present application. Claims 30-34 have been withdrawn from consideration by the Examiner and claims 6-8, 13, 20, 21, 26-28, and 36-38 have been cancelled by the above amendment. Claims 1, 5, 16, 17, 29, and 35 have been amended and new claims 39-41 have been added. The amendments, including the new claims, are supported by the specification and no new matter has been added. Reexamination of the application and reconsideration of the rejections are respectfully requested in view of the above amendments and the following remarks, which follow the order set forth in the Office Action.

A. Claim rejections--35 U.S.C. § 112

Claims 1-29 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that "predicting a retention time of the compound of interest from a preparative scale HPLC column" renders the claim indefinite.

The language has been removed from all claims in which this language was present. Applicants therefore respectfully request that the Examiner withdraw this rejection.

B. Claim rejections--35 U.S.C. §§ 102 and 103

Claims 1-29 and 35-38 were rejected under 35 U.S.C. § 102 (a) and/or (e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 (a) as obvious over Collins (WO 01/90739). This rejection is traversed for the reasons explained below.

Applicants initially note that Collins (WO 01/90739) is not a proper prior art reference under 35 U.S.C. § 102 (e), which states that "an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States *only if the international application designated the United States* and was published under Article 21(2) of such treaty in the English language" (emphasis added). Collins (WO 01/90739) did not designate the United States, as is clear from the face of the publication. Therefore, Collins is not a proper prior art reference under 35 U.S.C. § 102 (e) to the present application.

Collins is directed to isolating one or more components of a chemical mixture using chromatographic separation. Embodiments of the invention enable a desired component to be isolated at an accelerated rate compared to conventional chromatographic separations. Embodiments of the invention effect elution of the desired component through a column (e.g., a preparative HPLC column) at a given retention time, which retention time may be

selected (e.g., pre-selected) by a user. Embodiments of the invention enable the retention time of the desired component to be predicted and/or controlled. *(See p. 2, lines 22-29).*

In a first step in Collins, a desired component of a chemical mixture is identified. *See p. 8, line 15.* In a second step, a first retention time and/or corresponding first set of chromatographic parameters is/are identified for the desired component. *See p. 8, lines 25-26.* In a third step, a second set of chromatographic parameters is determined based on the first retention time and/or the corresponding first set of chromatographic parameters. *See p. 9, lines 1-2.* In a fourth step, the desired component is isolated. *See p. 9, lines 12-14.*

The third step in Collins comprises determining preparative chromatographic parameters based on the analytical retention time and the corresponding analytical chromatographic parameters. The preparative chromatographic parameters are determined to enable the desired component to be isolated at an accelerated retention time using a preparative HPLC column. *(See p. 11, lines 14-17).*

The third step in Collins involves a plurality of steps. First, a scaled-up retention time of the desired product on the preparative HPLC column is determined based on a scale-up from the analytical HPLC column to the preparative HPLC column. This scale-up accounts for the larger length and/or diameter of the preparative HPLC column and/or any change in linear velocity of mobile phase while directly translating one or more of the analytical chromatographic parameters. The scaled-up retention time indicates a retention time associated with elution of the desired component through the preparative HPLC column if one or more of the analytical chromatographic parameters are preserved (e. g., if the analytical initial mobile phase composition, the analytical final mobile phase composition, and the analytical gradient steepness parameter are used for elution through the preparative HPLC column). *(See p. 11, line 31 - p. 12, line 11).* After determining a scaled-up retention time, a scaled-up gradient time interval for the preparative HPLC column is determined. As with the scaled-up retention time, the scaled-up gradient time interval is determined while preserving one or more of the analytical chromatographic parameters (e. g., the analytical initial mobile phase composition, the analytical final mobile phase composition, and the analytical gradient steepness parameter from the analytical chromatographic separation). *(See p. 13, lines 13-18).* Then, using the scaled-up retention time and the scaled-up gradient time interval values, preparative chromatographic parameters are determined to effect separation/isolation of the desired component at an accelerated retention time using the preparative HPLC column. *(See p. 13, line 32-p. 14, line 2).*

In contrast to Collins, independent claims 1, 5, 17, and 35 of the present application each recite a method of separating a compound (or compounds) of interest from a mixture (or mixtures) that involves, for each compound:

determining a retention time of a compound of interest on an analytical HPLC column;

predicting a retention time of the compound of interest from a preparative scale HPLC column using a predetermined static correlation function between retention time on the analytical HPLC column and retention time on the preparative scale HPLC column along with the determined retention time of the compound of interest on the analytical HPLC column;

selecting a window of time around the predicted retention time within which the compound is expected to elute;

subjecting all or a portion of the remaining mixture to a preparative scale HPLC system comprising the preparative scale HPLC column; and

collecting at least a portion of the compound of interest using the selected window of time.

As explained in the application, a "'correlation function' may be a correlation (linear or otherwise) of retention time on an analytical HPLC column (with specified components) versus retention time on a preparative scale HPLC column (with specified components)." *See p. 9, paragraph [0033].* Therefore, when using a correlation function according to the present invention, the analytical HPLC column will have predetermined components and the preparative scale HPLC column will have predetermined components. As explained in the application, the components of the analytical HPLC system (e.g., the column, stationary phase, and mobile phase) and the conditions used with the analytical HPLC system (e.g., pressure and flow rate) may vary with the particular compound and mixture to be introduced into the system *(See p. 6, paragraph [0027])*, and the components of and the conditions used with the preparative scale HPLC system may also vary with the particular compound and mixture to be introduced into the system. *See p. 11, paragraph [0038].*

As also explained in the application, when using a **static correlation function**, the **components and conditions** used during the analytical HPLC and the preparative scale HPLC (e.g., flow rate, mobile phase, column size, etc.) are constant, and such components and conditions are therefore predetermined when performing methods of separating a compound or compounds from a mixture or mixtures using a static correlation function as presently claimed. *(See, e.g., paragraphs [0036] and [0037] on pages 10-11 as well as Example 1 on pages 13-15 illustrating the use of a linear static correlation function).* As made clear in the application, "**a static correlation function (e.g., a linear correlation function)**" includes "**factors that are constant ... (e.g., flow rate, mobile phase, column size, etc.)**." *See paragraph [0036] on pages 10-11.* The "components and/or conditions used during the preparative scale HPLC (e.g., flow rate, mobile phase, etc.) could be

changed" when using a dynamic correlation function, but cannot be changed when using a static correlation (i.e., the components and conditions used during the preparative scale HPLC are constant and predetermined when using a static correlation function). *See paragraph [0036] on pages 10-11.*

After the retention time of the compound of interest is predicted using the predetermined static correlation function, a window of time is selected around the predicted retention time within which the compound is expected to elute. All or a portion of the remaining mixture is subjected to a preparative scale HPLC system comprising the preparative scale HPLC column, and at least a portion of the compound of interest is collected using the selected window of time. As explained in the application, the window of time is "a period of time before and after the predicted retention time ... that is expected to collect at least some, and preferably all or most of the compound of interest." *See page, 10, paragraph [0035].*

In order to anticipate a claim, each and every element as set forth in the claim must be found, either expressly or inherently, in a single prior art reference. MPEP § 2131. Collins does not teach or suggest, expressly or inherently, **predicting a retention time** of the compound of interest from a preparative scale HPLC column using a **predetermined static correlation function** between retention time on the analytical HPLC column and retention time on the preparative scale HPLC column, **selecting a window of time around the predicted retention time**, and **collecting** at least a portion of the compound from the preparative scale HPLC column **using the selected window of time** as recited in independent claims 1, 5, 17, and 35. As explained above, when using a static correlation function between retention time on an analytical HPLC and retention time on a preparative scale HPLC, the components and conditions to be used during the analytical HPLC and the preparative scale HPLC are constant and predetermined for both the analytical HPLC and the preparative scale HPLC. In Collins, **preparative chromatographic parameters** to isolate the component at an accelerated retention time using a preparative column **are determined based on the analytical retention time and the corresponding analytical chromatographic parameters**. *See p.11, lines 14-15.* The **desired component is isolated** in Collins by performing a preparative chromatographic separation **using the determined preparative chromatographic parameters**, and the desired component may be isolated at the accelerated retention time, and may be collected within a time interval that includes the accelerated retention time. *See, e.g., p. 15, lines 17-25.* Unlike the present claims, which require that at least a portion of the compound of interest be collected using a selected window of time around a retention time that is predicted using a **static correlation**

function, Collins collects the desired component using a retention time (or a time interval) associated with the **determined** chromatographic parameters.

Therefore, in view of the above, Collins does not anticipate independent claims 1, 5, 17, or 35 or any claims depending therefrom. Applicants respectfully request that the 35 U.S.C. § 102 (a) and § 102 (e) rejection of pending claims 1-5, 9-12, 14-19, 22-25, 29, and 35 be withdrawn.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143.

As discussed above, Collins does not teach or suggest using a predetermined static correlation function to predict a retention time for a compound of interest on a preparative scale HPLC column and then collecting at least a portion of the compound of interest from the preparative scale HPLC column using a selected window of time around the predicted retention time. Rather, Collins teaches determining preparative chromatographic parameters based on the analytical retention time and the corresponding analytical chromatographic parameters and then isolating the component at a time interval that includes the accelerated retention time associated with the determined preparative chromatographic parameters. Therefore, claims 1-5, 9-12, 14-19, 22-25, 29, and 35 are not obvious over Collins because each element of the claims is not taught or suggested by Collins.

Furthermore, there is no suggestion or motivation to modify Collins to achieve the claimed invention. "Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1316-17 (Fed. Cir. 2000). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." *Id.* at 1317 (citations omitted). The Examiner has not pointed to any suggestion or motivation to modify Collins such that at least a portion of a compound of interest is **collected** from a preparative scale HPLC column **using a selected window of time around a retention time predicted using a predetermined static correlation function**. In addition, nowhere in Collins is there any suggestion or motivation to modify the teachings therein in such a manner. As discussed above, Collins discloses that the desired component is collected at an accelerated retention time (or time interval) by performing a preparative chromatographic

separation using **preparative chromatographic parameters that *are determined*** based on the analytical retention time and the corresponding analytical chromatographic parameters. Therefore, claims 1-5, 9-12, 14-19, 22-25, 29, and 35 are not obvious over Collins because there is no suggestion or motivation provided in Collins or elsewhere to modify Collins such that at least a portion of a compound of interest is collected from a preparative scale HPLC column using a selected window of time around a retention time predicted using a predetermined static correlation function.

In view of the above, Applicants respectfully request that the 35 U.S.C. § 103 rejection of pending claims 1-5, 9-12, 14-19, 22-25, 29, and 35 be withdrawn.

Claims 2, 3, 9, 10, 11, 14, 23, 24, 28, and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Collins (WO 01/90739) in view of Kibbey (U.S. Patent No. 5,670,054). Applicants respectfully traverse this rejection with respect to pending claims 2, 3, 9, 10, 11, 14, 23, 24, and 29 for the reasons given below. The rejection is moot with respect to cancelled claim 28.

Kibbey discloses an automated method of sample identification, purification and quantitation wherein a first HPLC column with defined operating parameters is used to separate a small portion of an impure mixture into its constituent components; the individual components corresponding to the eluting zones of the separated mixture are characterized by mass spectrometry; the chromatographic and mass spectroscopic data generated are stored in digital format, for example one compatible with commercial chromatography software, and the data is used to guide the purification of the remaining sample; the remaining sample is injected on a semi-preparative, or preparative HPLC column; an analog detector output of the semi-preparative, or preparative HPLC system is digitized and evaluated electronically with the previously generated chromatographic and mass spectroscopic data; when elution of a sample component peak corresponding to a desired product peak is sensed, a mechanically actuated, liquid switching value (i.e., a pneumatic or electronic switching valve) is actuated to divert the column eluate from waste to a fraction collection device; and when the end of product peak elution is sensed, the switching valve is actuated to divert the column eluate back to waste collection. *See column 5, lines 29-51.*

Neither Collins nor Kibbey, alone or in combination, teach or suggest all the limitations of independent claims 1, 5, or 17. Neither document, alone or in combination, teaches or suggests using a predetermined static correlation function to predict a retention time for a compound of interest on a preparative scale HPLC column and then collecting at least a portion of the compound of interest using a selected window of time around the predicted retention time as recited in claims 1, 5, and 17. Therefore, Applicants respectfully

request that the 35 U.S.C. § 103 rejection of pending claims 2, 3, 9, 10, 11, 14, 23, 24, and 29 (which ultimately depend from claim 1, claim 5, or claim 17) be withdrawn.

Claims 7, 8, 21, 37, and 38 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Collins (WO 01/90739) in view of Afeyan (U.S. Patent No. 6,344,172). As claims 7, 8, 21, 37, and 38 have been cancelled, this rejection is now moot.

Claims 17-29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Collins (WO 01/90739) in view of Zambias (U.S. Patent No. 5,766,481). Applicants respectfully traverse this rejection with respect to pending claims 17-19, 22-25, and 29 for the reasons given below. The rejection is moot with respect to cancelled claims 20, 21, and 26-28.

Zambias relates to a method for the processing of molecules by determining one or more selection parameters for a plurality of molecules; selecting a compatible grouping of molecules based on the selection parameters to form a set; forming a mixture of molecules of interest from the set; and resolving the mixture to fractionate the molecules of interest. The preferred method utilizes an HPLC chromatography column to resolve and purify molecules which have different retention times. *See Abstract.*

Neither Collins nor Zambias, alone or in combination, teach or suggest all the limitations of independent claim 17. Neither document, alone or in combination, teaches or suggests using a predetermined static correlation function to predict a retention time for each compound of interest on a preparative scale HPLC column and then separately collecting at least a portion of each compound of interest verified to be present using a selected window of time around each predicted retention time as recited in claim 17. Therefore, Applicants respectfully request that the 35 U.S.C. § 103 rejection of pending independent claim 17 and pending claims 18-19, 22-25, and 29 (which ultimately depend from claim 17) be withdrawn.

Claims 23, 24, 28, and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Collins (WO 01/90739) in view of Zambias (U.S. Patent No. 5,766,481) as applied to claims 17-29, and further in view of Kibbey (U.S. Patent No. 5,670,054). Applicants respectfully traverse this rejection with respect to pending claims 23, 24, and 29 for the reasons given below. The rejection is moot with respect to cancelled claim 28.

Neither Collins, Zambias, nor Kibbey, alone or in combination, teach or suggest all the limitations of independent claim 17. None of the documents, alone or in combination, teach or suggest using a predetermined static correlation function to predict a retention time for each compound of interest on a preparative scale HPLC column and then separately

collecting at least a portion of each compound of interest verified to be present using a selected window of time around each predicted retention time as recited in claim 17. Therefore, Applicants respectfully request that the 35 U.S.C. § 103 rejection of pending claims 23, 24, and 29 (which ultimately depend from claim 17) be withdrawn.

Claim 21 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Collins (WO 01/90739) in view of Zambias (U.S. Patent No. 5,766,481) as applied to claims 17-29, and further in view of Afeyan (U.S. Patent No. 6,344,172). As claim 21 has been cancelled, this rejection is now moot.

Conclusion

For the foregoing reasons, pending claims 1-5, 9-12, 14-19, 22-25, 29, 35, and 39-41 are considered allowable. A Notice to this effect is respectfully solicited. If any questions remain, the Examiner is invited to contact the undersigned attorney at the number given below.

Respectfully submitted,
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Mark-up of Amended Claims 1, 5, 16, 17, 29, and 35

1. (Amended) A method of separating a compound of interest from a mixture, the method comprising the steps of:

(a) providing a mixture containing a compound of interest, the compound of interest having an expected mass;

(b) subjecting a portion of the mixture to a separation using an analytical HPLC column to produce an eluate stream;

(c) analyzing the eluate stream using a mass spectrometer to determine a retention time of the compound of interest on the analytical HPLC column;

[(d) predicting an elution time for the compound of interest from a preparative scale HPLC column by:

(1) predicting a retention time of the compound of interest from the preparative scale HPLC column using a predetermined correlation function between the analytical HPLC column and the preparative scale HPLC column along with the determined retention time of the compound on the analytical HPLC column; and

(2) selecting a window of time around the predicted retention time within which the compound is expected to elute;]

(d) predicting a retention time of the compound of interest from a preparative scale HPLC column using a predetermined static correlation function between retention time on the analytical HPLC column and retention time on the preparative scale HPLC column along with the determined retention time of the compound on the analytical HPLC column;

(e) selecting a window of time around the predicted retention time within which the compound is expected to elute;

(f) [(e)] subjecting all or a portion of the remaining mixture to a preparative scale HPLC system comprising [a] the preparative scale HPLC column, an HPLC compatible detector, and a fraction collector; and

(g) [(f)] collecting at least a portion of the compound of interest using the fraction collector, the fraction collector being activated upon detection of a peak by the HPLC compatible detector within the [predicted elution] selected window of time.

5. (Amended) A method of separating a compound of interest from a mixture, the method comprising the steps of:

(a) providing a mixture containing a compound of interest, the compound of interest having an expected mass;

(b) subjecting a portion of the mixture to a separation using an analytical HPLC column to produce an eluate stream;

(c) analyzing the eluate stream using a mass spectrometer to determine a retention time of the compound of interest on the analytical HPLC column;

[(d) predicting an elution time for the compound of interest from a preparative scale HPLC column using the determined retention time of the compound of interest on the analytical HPLC column;]

(d) predicting a retention time of the compound of interest from a preparative scale HPLC column using a predetermined static correlation function between retention time on the analytical HPLC column and retention time on the preparative scale HPLC column along with the determined retention time of the compound on the analytical HPLC column;

(e) selecting a window of time around the predicted retention time within which the compound is expected to elute;

(f) [(e)] subjecting all or a portion of the remaining mixture to a preparative scale HPLC system comprising [a] the preparative scale HPLC column; and

(g) [(f)] collecting at least a portion of the compound of interest using the [predicted elution] selected window of time.

16. (Amended) The method of claim 5 wherein the collection step (g) [(f)] is performed without the use of an HPLC compatible detector.

17. (Amended) A method of separating compounds of interest present in a plurality of reaction product mixtures, the method comprising the steps of:

(a) providing a plurality of reaction product mixtures, each mixture expected to contain a compound of interest having an expected mass;

(b) separately subjecting a portion of each reaction product mixture to a separation using an analytical HPLC column to produce a plurality of eluate streams;

(c) analyzing each eluate stream using a mass spectrometer to verify that the eluate stream contains a compound with an expected mass and to determine a retention time of each compound with an expected mass on the analytical HPLC column;

[(d) predicting an elution time for each compound with an expected mass from a preparative scale HPLC column using the determined retention time for each compound with an expected mass on the analytical HPLC column;]

(d) predicting a retention time of each compound with an expected mass on a preparative scale HPLC column using a predetermined static correlation function between retention time on the analytical HPLC column and retention time on the preparative scale HPLC column along with the determined retention time of each compound on the analytical HPLC column;

(e) selecting a window of time around each predicted retention time within which each compound with an expected mass is expected to elute;

(f) [(e)] separately subjecting all or a portion of each remaining mixture verified to contain a compound with the expected mass to a preparative scale HPLC system comprising [a] the preparative scale HPLC column and a fraction collector; and

(g) [(f)] separately collecting at least a portion of each compound verified to be present with the fraction collector using the [predicted elution] selected window of time for each compound.

29. (Amended) The method of claim [28] 23 wherein [the preparative scale HPLC system includes a fraction collector that collects at least a portion of the compound of interest,] the fraction collector [being] is activated upon detection of a peak by the HPLC compatible detector within the [predicted elution] selected window of time.

35. (Amended) A method of separating a compound of interest from a mixture, the method comprising the steps of:

(a) providing a mixture containing a compound of interest;

(b) subjecting a portion of the mixture to a separation using either (1) thin layer chromatography to produce one or more spots or zones or (2) an analytical HPLC column to produce an eluate stream;

(c) determining either (1) an Rf value for the compound of interest by analyzing the one or more spots or zones or (2) a retention time of the compound of interest on the analytical HPLC column by analyzing the eluate stream;

[(d) predicting an elution time of the compound of interest on a preparative scale HPLC column using either (1) the determined Rf value for the compound of

interest or (2) the determined retention time of the compound of interest on the analytical HPLC column;]

(d) predicting a retention time of the compound of interest from a preparative scale HPLC column using either:

(1) a predetermined static correlation function between Rf value from the thin layer chromatography and retention time on the preparative scale HPLC column along with the determined Rf value of the compound of interest, or

(2) a predetermined static correlation function between retention time on the analytical HPLC column and retention time on the preparative scale HPLC column along with the determined retention time of the compound of interest on the analytical HPLC column;

(e) selecting a window of time around the predicted retention time within which the compound of interest is expected to elute;

(f) [(e)] subjecting all or a portion of the remaining mixture to a preparative scale HPLC system comprising [a] the preparative scale HPLC column; and

(g) [(f)] collecting at least a portion of the compound of interest using the [predicted elution] selected window of time.